Issue Concerning Sequence Compliance

The specification stands objected to because the Examiner asserts that Applicants have failed to adhere to Sequence Listing rules. Applicants have reviewed the specification and could not determine any sequences that need SEQ ID NO. Applicants request the Examiner to identify any possible rule violations more specifically.

With finding the specification in compliance, Applicants respectfully request withdrawal of the objection.

Issue Concerning Specification

The Examiner has noted minor informalities that exist in the specification. MPEP §608.01(a) recites the preferred layout and content for patent application. "These guidelines are suggested for the applicant's use." Applicants have amended the specification to recite proper subject headings; however, Applicants have not rearranged the specification to follow the suggested order. Applicants believe the specification is clearly written and is sufficient as ordered and that rearrangement would only cause confusion at the printing stage.

Applicants respectfully request withdrawal of the objection to the specification.

Issue Under 35 U.S.C. §101

Claim 15 stands rejected under 35 U.S.C. §101 as allegedly claiming an invention directed to non-statutory subject matter. The Examiner asserts that the pestivirus mutant encompasses naturally occurring pestivirus mutants that have not been isolated.

Applicants have amended the claims by inserting the word "isolated." Applicants respectfully request withdrawal of the 35 U.S.C. §101 rejection.

Issue Under 35 U.S.C. §112

Claims 15-24 and 35-47 stand rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. The Examiner asserts that the claim language of claims 15, 19, 20, 21 and 22 contain language that is vague and indefinite.

Applicants have amended claims to address the §112 issues. In claim 15, Applicants clarify that the 5'-GUAU sequence is retained as described on page 4, fourth paragraph. In claims 19 and 20, Applicants have clarified the language. In claim 21, Applicants have added the language, "after said deletion" to clarify that the 5'-GUAU sequence is retained as described on page 4. In claim 22, Applicants have removed the phrase "if present."

The Examiner's confusion appears to stem from the fact SL-8 and Δ2-31 appears to disrupt the 5'-GUAU requirement. This assumption is incorrect. As can be seen from figure 6a, the GUAU

sequence is present. It is also present in SL-8 as can be seen from Figure 5. (GUAUAC are denoted as nucleotides 25-30, while nucleotides 1-24 have been deleted.) As can be seen from figure 1, the first four nucleotides of the sequence of the stem loop are GUAU, but so are nucleotides 25-28. Thus, when nucleotides 1-24 are deleted the sequence starts with GUAU again (former nucleotides 25-28). And, when nucleotides 2-31 are deleted, the GUAU sequence is re-created, since nucleotide 1(G) is now linked to nucleotides 31-33 (UAU).

It does not matter where the G-U-A-U nucleotides originally were, they should just be in this order after the mutations have been made.

Claim 21, is based on the specification, page 5, lines 17-22. Applicants disclose mutants lacking all of the stem loop (5-73). These deleted stem loops have a sequence AU or CCU inserted between GUAU and the 5′ end of the IRES. Consequently the 5′ terminal sequence in these mutants is either GUAUAU or GUAUCCU.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

Issue Under 35 U.S.C. §112, First Paragraph

Claims 15-24 and 35-47 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly having an insufficient written description. The Examiner asserts that the specification allegedly fails to disclose a pestivirus mutant with a single point mutation in either stem loop or a mutant with both stem

loops completely deleted. The Examiner asserts that insufficient guidance is given to determine which mutations will result in an attenuated mutant. Applicants respectfully traverse this assertion.

In the experimental part of the description many of these mutants were tested, some had parts of the stem-loop structure deleted while other contained substitutions. For example, SL-2, 3, 5, 6 and 7 contained deletions or substitutions of only 2 or 3 nucleotides and already showed the desired effect. The mutants with bigger deletions, such as Δ2-31, Δ5-57 and Δ5-73 were preferred.

The region in which the mutations were made contains stem-loop structures. These structures are held together by hybridizations between different regions within the structure. As discussed above, the confusion appears to stem from the fact SL-8 and Δ2-31 appears to disrupt the 5'-GUAU requirement. This assumption is incorrect. Yes, the original 5'-GUAU is changed, but the resulting sequence still retains a 5'-GUAU. The UAU is just from further down the sequence.

Claim 21, is based on the specification, page 5, lines 17-22. Applicants disclose mutants lacking all of the stem loop (5-73). These deleted stem loops have a sequence AU or CCU inserted between GUAU and the 5' end of the IRES. Consequently the 5' terminal sequence in these mutants is either GUAUAU or GUAUCCU.

Applicants submit with this amendment a 35 U.S.C. §1.132 Declaration by Dr. Birgit Makoschey. In this §132 Declaration, Dr. Makoshey describes experimental results that address these

matters and provide further evidence for the invention.

The objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). "The subject matter of the claim need not be described literally . . . in order for the disclosure to satisfy the description requirement." MPEP §2163.02.

As stated above, Applicants must describe the present invention clearly to allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. Applicants have clearly disclosed each element of the invention.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejection.

Issue Under 35 U.S.C. §112, First Paragraph

Claims 15-24 and 35-47 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly having an insufficient written description. The Examiner asserts that the specification would not convey to a skilled artisan that every pestivirus could be altered and have similar results.

The Examiner notes that the working examples demonstrate unpredictability between mutations, such as BVDV-1 and CP7-5A on page 10. More importantly, the Examiner recites the specification on page 2, lines 9-11 which states "it is still not

region(s) of the genome should and can be modified to lead to a safe and effective vaccine strain."

In the specification, several criteria for determining attenuation are given. For example, on page 3-4, Applicants state that the plaque size should at least be 50% reduced, resulting in an average plaque size of about 0.2-2mm. Moreover, on page 6 it is stated that a reduced ability to replicate can be ascertained with the mutants measuring specific infectivity (the $TCID_{50}$). On page 14 it is stated that, for practical purposes, the mutants should grow preferably to titers of at least 10^5 $TCID_{50}$/ml. Thus, ample data exists for the skilled person to test whether his or hers mutants fulfill the criteria posed on mutants according to the invention.

As for the concern of the "unpredictability of the art" and the "lack of working examples" regarding any immunized animals, the Examiner refers to page 2 of the specification and states that "it is still not known which region(s) of the genome should and can be modified to lead to a safe and effective vaccine." Applicants have identified a region which can be mutated and lead to an attenuated phenotype.

The Examiner objects to the claims also since they are not limited to any specific pestivirus strain. The Examiner asserts that a multitude of different pestiviruses exists. Applicants traverse this assumption.

Pestiviruses are very similar, especially in their genomic organization. For example, CSFV and BVDV are even serologically cross-reactive, meaning that antibodies raised against one virus

B

Version with Marking to Show Changes Made

In the Specification

The following subject heading has been added before the paragraph beginning on page 1, line 1:

--Field of the Invention--

The following subject heading has been added before the paragraph beginning on page 1, line 7:

--Background of the Invention--

The following subject heading has been added before the paragraph beginning on page 2, line 17:

--Brief Summary of the Invention--

The following subject heading has been added before the paragraph beginning on page 2, line 27:

--Detailed Description of the Invention--

The following subject heading has been amended on page 16, line 20 with the following:

[LEGENDS TO THE FIGURES] --Brief Description of the Drawings--

In the Claims

Please amend the claims as follows:

15. (Amended) An attenuated isolated pestivirus mutant having a

growth-restricted phenotype relative to a wild-type pestivirus, said mutant, comprising:

one or more mutations of stem loops 1a and/or 1b of the 5' nontranslated region (NTR) of the pestivirus genome, and

wherein the mutated 5' end of the genome [comprises] conserves the nucleotide sequence 5'-GUAU and expression of a viral poly protein from said genome is under the control of a homologous internal ribosome entry site (IRES).

16. (Amedned) The isolated pestivirus mutant of claim a, wherein said growth-restricted phenotype is characterised by a small plaque size phenotype.

17. (Amended) The isolated pestivirus mutant of claim 15, wherein the mutant comprises more than one mutation in the stem loops 1a and/or 1b.

18. (Amended) The isolated pestivirus mutant of claim 15, wherein the one or more mutations is a deletion of one or more nucleotides.

19. (Amended) The isolated pestivirus mutant of claim 15, wherein the one or more [notations] mutations is a deletion of stem loop 1a[, or a part thereof].

20. (Amended) The isolated pestivirus mutant of claim 18, wherein the one or more mutations is a deletion of stem loop 1a and [part

of] a deletion in stem loop 1b.

21. (Amended) The isolated pestivirus mutant of claim 18, wherein the mutation is a deletion of stem loops 1a and 1b, and wherein the nucleotide sequence after said deletion at the 5' end of the genome is GUAUAU or GUAUCCU.

22. (Amended) The isolated pestivirus mutant of claim 18, wherein the loop portion of stem loop 1b[, if present,] contains five adenosine (A) residues.

23. (Amended) The isolated pestivirus mutant of claim 15, wherein the pestivirus is bovine viral diarrhea virus (BVDV).

24. (Amended) The isolated pestivirus mutant of claim 23, wherein the pestivirus is BVDV-1 or BVDV-2.

35. (Amended) A vaccine, comprising:

an immunogenically active isolated pestivirus mutant of claim 15 and

a pharmaceutically acceptable carrier or diluent.

40. (Amended) A vaccine, comprising:

an immunogenically effective dosage of the isolated pestivirus mutant of claim 15, and

a pharmaceutically acceptable carrier and diluent.